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FINAL REPORT

Contract Nonr-248(34) (NR 101-241)

Between the Office of Naval Research, Department of the Navy,

and The Johns Hopkins University

October 1, 1946 - June 30, 1962



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## AIMS

Contract N5ori-166, Task VIII, between The Johns Hopkins University and the Office of Naval Research, was effective from October 1, 1946 to June 30, 1954. It was succeeded by contract Nonr 248(34) which ran from July 1, 1954 through June 30, 1962. This was a continuing study entitled simply Study of Nerve and Muscle Function, identified as project NR 113-241 until December 31, 1957 and as project NR 101-241 from January 1, 1958 until its termination.

The aim of the project, stated in January 1947 in a report to ONR by the late Joseph L. Lilienthal, first investigator under the contract, was "application of several different analytical technics to a study of dysfunction of the nerve and muscle unit. The correlations will be studied between (1) the physical accompaniments of activity: electrical potential and muscular contraction and (2) the chemical phases with particular reference to the muscle enzyme systems providing the energy for contraction (redox and phosphorylating). Dysfunction will be studied as it appears in man in the clinic (e.g., dystrophy, myasthenia, myotonia, hyperthyroidism, hypoadrenalism, atrophy, etc.) and as it may be produced in the experimental animal (e.g., denervation, spasticity, electrolyte disturbances and bacterial toxins such as botulinus and diphtheria)."

The progress report for 1961 said the aim was "to study metabolic, electrical, and mechanical events in neuromuscular function in man and the experimental animal in order to understand these processes and thereby to gain some insight into mechanisms involved in clinical manifestations of disturbances of these functions." There is remarkably little difference in these two statements of purpose, separated by 15 years. This is not so much due to our single-mindedness as it is a tribute to ONR in accepting statements of purpose so broad and general that we were able to move freely within a vast framework to follow, in clear conscience, whatever leads seemed to us most promising or most satisfying. As a result of this freedom this project produced work reported in 105 articles, covering a number of subspecial areas, through avenues that diverged and sometimes converged again. I am convinced that we could not have had this productivity, quite apart from the question of whether or not any of our efforts were meritorious, without the farsightedness of ONR and the wisdom and sympathy of individual officers of ONR with whom we dealt. During the formative period of this laboratory, its financial support was largely supplied by this contract. Without it, this laboratory could not have grown in the directions in which it did. Later when the laboratory grew so that a majority of its funds came from sources outside ONR, it was the ONR contract that permitted, in large measure, the flexibility that has been vital to our continued development.

PERSONNEL

The names of 25 investigators, listed below in order of seniority on this contract, have been cited as associated with this contract. Two, Drs. Lilienthal and Buka, are now dead. Nineteen are still engaged in research and, of these, fourteen are full-time members of a university faculty. The median number of investigators associated with the contract each year is 6. The 25 are:

J. L. Lilienthal, Jr., K. L. Zierler, D. Grob, A. M. Harvey, B. P. Folk, L. W. Jarcho, R. Buka, C. Eyzaguirre, D. Baldwin, B. Berman, R. Andres, R. Dowben, R. Levy, H. Anderson, W. N. Stainsby, B. McArdle, G. Cader, A. Ghrayyib, J. T. Fales, J. C. Harvey, M. A. Baltzan, S. R. Heisey, H. W. Dickerman, D. Rabinowitz and G. Gey, Jr.

RESULTS

The following account of work done under this contract is a brief narrative summary designed to show the interrelations of various activities within the project. Details are found in the published papers indicated in parentheses by numbers corresponding to those listed in the Bibliography of Technical Reports herewith appended.

Our purpose was simply to learn as much as we could about the electrical, mechanical and metabolic processes occurring in muscle. Test systems have varied with the demands of the problem, from the simplest hypothetical, mathematical models to complex experiments of nature in spontaneous disease of man.

The project had its origin in Dr. Lilienthal's interest in the myoneural junction. Some of the early studies dealt, therefore, with neuromuscular transmission, particularly with the action of curare and curare-like substances (1,11,12,14,19). My entree into the project was a concern with creatinuria, long the clinical hallmark of muscle disease. It soon became apparent that understanding creatinuria required not only knowledge of the role of muscle but also facts on renal handling of creatine (8). This problem led to examination of renal function in the dog and in man, to use of the kidney as an organ in which mechanism of movement into and out of cells could be studied, and to some involvement in clinical problems related to renal disease (63). (Undoubtedly, our experience with classical renal clearance techniques was important in leading to development of methods for studying metabolism in the human forearm, which has been a major preoccupation in recent years.)

Studies of renal handling of creatine revealed that some creatinurias, notably puerperal creatinuria, are primarily due to decreased renal tubular reabsorption of creatine (8) while

others are due simply to overflow, that is, to reduction in muscle mass in the presence of continuing synthesis of creatine. Studies of factors modifying tubular reabsorption of creatine led to investigation of certain hormonal effects on the kidney (2) and in muscle (2,17), and these, too, helped direct us to more detailed studies of endocrine action on muscle that we took up later.

Contemporaneously with our studies on creatinuria we were engaged in examining myotonia. Experimental repetitive phenomena, resembling myotonia to some extent, were produced in the rat by 2,4-dichlorphenoxyacetate (5). This led to study of other veratrinic agents (6) and to the fact that potassium potentiated veratrinic action. This was one of the observations that focused our attention on K and on ions, in general. Our need to know ionic K concentration in interstitial fluid bathing muscle required measurement of distribution of K and Na between serum and extracellular fluid (4). We found that Donnan ratios existed and that, within limits of analytical error, all serum K was ionized.

The studies of repetitive phenomena raised questions about the reasons for some curious details of compound action potentials in muscle. Accordingly maps were constructed of spread of excitation over skeletal muscle (18). Action potentials spread in both directions along a fiber from the myoneural junction. When a fiber has two myoneural junctions at opposite ends, the action potentials obliterate one another in mid-fiber. An offshoot of this were observations on the sites of origin and velocity of propagation of fibrillary potentials of denervated muscle (24,32,35), and to this end a metal-filled microelectrode was designed and built (29).

The myopathy and creatinuria produced by dietary lack of vitamin E led to a series of studies designed to probe the mechanism of action of tocopherol (3,7,9,23,25,26,27,28). These produced a number of interesting observations, some were probably the results of the surface-active effects of α-tocopheryl phosphate and not of tocopherol. Others could not be explained in this way. Although our studies led us to conclude that tocopherol seemed to act at the level of phosphoglucomutase, a result since confirmed in two other laboratories, the result was intellectually unsatisfactory in that it made no obvious use of the powerful anti-oxidant property of α-tocopherol.

In the course of studies on tocopherol, excised rat diaphragms were used as test systems. It was discovered that glycolytic enzymes diffused from the diaphragm into the medium (25). The fact that molecules of such large size could diffuse out of muscle provoked a series of experiments designed to examine factors modifying permeability of muscle, not only in the diaphragm but also in limb muscles in which no fibers are dam-

aged (42,43,44,59,60,62,64,68,69,74,87). These studies are interpreted as demonstrating that the barrier to diffusion is versatile and labile, influenced by the metabolism of the cell it envelopes. From them has been projected a model of the cell membrane as a dynamic structure, in opposition to the pore theory.

Closely related to studies of membrane permeability to large molecules are studies of permeability to ions and studies of electrical phenomena. We wondered if mammalian skeletal muscle really behaved at rest as though it were a potassium battery and, accordingly, we devised ways of altering K concentrations in situ to achieve a new steady state (46,55,66,72). The data suggested that the contribution of K to the resting membrane potential in living mammalian muscle was quantitatively less than it appeared to be for the giant axon of the squid but there were uncertainties about the exact composition of fluid bathing muscle in situ and not subject to direct chemical analysis.

The notion that the resting membrane potential of mammalian skeletal muscle was determined by more than the K equilibrium potential proved useful in our studies of the mechanism of insulin action. Here, we asked why insulin, administered to the intact animal, caused a fall in serum K concentration, apparently secondary to net K uptake by muscle. We found that insulin increased the resting membrane potential of rat skeletal muscle (61,75,77,78) and increased muscle K content even when glucose was not present (76,79). This was associated with reduced K flux in both directions, but outflux was reduced to a greater extent than influx (81,82). When external chloride concentration was decreased, insulin neither hyperpolarized nor caused K accumulation, but it still reduced K flux, although now reduced influx equalled reduced outflux. The hypothesis from these observations is that insulin alters the muscle membrane so as to make it relatively more cationic, accelerating transmembrane movement of anions and reducing transmembrane movement of cations. At the same time insulin deforms the membrane making it more permeable to a variety of substances (64). The effect on glucose uptake can be explained without evoking a hypothetical glucose carrier, simply on the basis of removing barriers to diffusion. This consideration led to kinetic analysis of poorly-permeable passive systems with formulation of a new hypothesis to explain data often interpreted as suggesting presence of a carrier (84,90).

Early in our studies of muscle in human disease we used two of the techniques then available for inference of quantitative change in metabolism: chemical analysis of body fluids and of muscle samples obtained by biopsy (4,10,21,22). We evolved a system of chemical analysis and proposed and used a chemical reference base (non-collagen nitrogen) that seems to

have been helpful to others.

However, for sometime we had been dissatisfied with the value of static chemical analysis of excised muscle and sought a method for attacking problems of muscle metabolism in intact man. Our earlier experience with renal clearances, which are examples of a use of the Fick principle, suggested using the Fick principle in the human forearm. We determined to measure metabolism by measuring arteriovenous concentration differences and forearm blood flow. Because we planned to have catheters in the brachial artery and antecubital veins for sampling for measurement of metabolites, we thought of using the same samples to measure blood flow by some indicator-dilution principle. First, we validated the method for measuring blood flow and then measured it (16,20,31).

In order to understand the method we explored the underlying principle (33,71,95,96,105). This led to extension of the Fick principle to include certain non-steady states (91).

After validating the blood flow method, we examined some aspects of basal metabolism of the forearm. We found brisk $O_2$ uptake, lactic acid production adequate to account for half the glucose uptake, and glucose uptake adequate to account for only about 10 per cent of $O_2$ uptake (34,37,39,40,45,48,49). Because the respiratory quotient of the forearm was about 0.7 we suggested that most of the stuff oxidized by resting human muscle in situ is lipid and that the probable lipids were those making up the free fatty acid (FFA) fraction (48). It had not been possible to prove this directly until very recently when we were able to eliminate FFA production by forearm adipose tissue (by use of insulin) and so unmask FFA uptake by forearm muscle (104).

During the mid- and late-morning hours when our studies of the forearm were done usually, K leaked in the net from forearm muscle to blood (41). Because K must sometime return to muscle, diurnal cycling of K movement was suspected, and this turned out to occur (57). We were lucky enough to have had an opportunity to study familial periodic paralysis at this time and demonstrated in them an exaggerated diurnal movement of K (47, 58).

An advantage and a handicap of this method of studying forearm metabolism is that the forearm is not simply muscle but contains, of course, other tissues. Concentrations of various metabolites in blood from forearm veins draining different tissues are, therefore, not necessarily uniform (85,94). However, this provides an opportunity to study adipose tissue metabolism as well as muscle metabolism, an advantage exploited in several ways.

Another advantage of this technique is that it is possible to inject into the brachial artery minute amounts of potent substances, achieving effective local concentrations. However, when these small amounts do escape into the general circulation, through forearm effluents, they are diluted about 100-fold so that they are apt to have no systemic effect. They do not, therefore, provoke any counter-regulatory systems. By this means we have studied the action of insulin, epinephrine, glucagon and growth hormone on the periphery.

Effects of insulin were not unexpected. Insulin induced glucose uptake and K uptake are not simultaneous. Insulin did not raise forearm $O_2$ uptake or RQ, whence it is concluded that insulin promotes glucose uptake but not its oxidation (52,54, 93). Insulin obliterated evidence of FFA release from forearm adipose tissue (97,104).

Glucagon had no peripheral effect.

Epinephrine caused, eventually, a steady increase in blood flow, no increase in glucose uptake, greatly increased lactate production, shift to K uptake and, most prominently of all, outpouring of FFA from forearm adipose tissue (88).

Growth hormone produces a shift to K uptake and increases FFA release and probably FFA uptake. The combination of growth hormone and insulin is most interesting. Insulin effect on glucose uptake by both muscle and adipose tissue is markedly reduced but the effect on FFA release is that of insulin (inhibition) and not that of growth hormone (increase). Thus, the effect of insulin on glucose uptake and its effect on FFA release are dissociated by growth hormone. This dissociation is seen also in active acromegaly, in Cushing's disease and in starvation, in which endogenous growth hormone activity is raised (98,99,102).

With respect to other kinds of insulin resistance, in common diabetes mellitus of maturity onset, response of forearm tissues to intra-arterial insulin is greatly diminished, that is, diabetes mellitus is a disease in which there is peripheral resistance to insulin. If the diabetic has been treated with insulin for several months or more there is almost complete nonresponsiveness to insulin, probably due to development of antibodies or plasma binding proteins (65).

In stable young obese subjects, there is evidence of spontaneous steady hyper-insulinism and a curious resistance to exogenous (intra-arterial) insulin (89,92,103). It is proposed that the hyperphagia of obesity leads to an adaptive hyperinsulinism and that this, in turn, leads ultimately to $\beta$-cell exhaustion and diabetes mellitus.

Besides injection of hormones, other substances can be introduced locally into the forearm. For example, by continuous intra-arterial infusion of glucose, we doubled forearm arterial glucose concentration without changing systemic glucose concentration and showed that, under these conditions in which endogenous insulin secretion is not provoked, there is no increase in glucose uptake (67).

Questions not yet suitable for inquiry of the forearm of man include those in which blood flow changes rapidly. Un happily this is what happens with muscle contraction. To answer some of these problems, experiments have used a normally-circulated isolated gastrocnemius-plantaris preparation in the dog.

In the course of standardizing the technique it was found that passive stretch of the muscle regularly diminished $O_2$ uptake and that release of stretch was not followed by payment of $O_2$ debt but by a rather accurate return to pre-stretch $O_2$ consumption (38,50). This observation went unexplained until we became interested in the relation between blood flow and muscle $O_2$ uptake (73). Venous obstruction reduces blood flow and $O_2$ uptake. Release of venous obstruction, unlike release of arterial occlusion, is followed by neither blood flow nor $O_2$ uptake debt repayment (80,101). This explains the effect of stretch, which mechanically obstructed venules.

The main purpose of the studies on the dog's hind limb has been to relate work and metabolism. To this end certain methods were devised (13,36,70). The results showed that $O_2$ uptake by skeletal muscle was not closely related to work but was a linear function of the number of stimuli, as though each arriving nerve impulse detonated a quantum of substrate, independent of work (51,56,83). For the past two years we have been developing a method to measure heat production by muscle in situ, with a view to getting a complete thermodynamic balance sheet.

From time to time the work of this laboratory has been reviewed (15,30,53,86,100).

Several reports of work begun under this contract will appear during the coming year and will be forwarded as technical reports.

## CONCLUSION

I must repeat part of my introduction. There is no doubt that I, personally, owe a great debt to ONR and that the wisdom with which ONR permitted us to move freely about our field was responsible for whatever productivity we may have had. If what we have accomplished has been worthwhile I hope it will be use-

ful as an example of what farsighted, flexible and sympathetic administration can accomplish in cooperation with investigators who must feel their way.

## BIBLIOGRAPHY OF TECHNICAL REPORTS


1. On certain vascular effects of curare in man: The "histamine" reaction. Bull. Johns Hopkins Hosp., 80: 299, 1947.

2. Sodium loss in man induced by desoxycorticosterone acetate. Am. J. Med., 4: 186, 1948.

3. On the antithrombic and antiproteolytic activity of alpha tocopheryl phosphate. Am. J. Physiol., 153: 127, 1948.

4. Distribution of potassium and sodium between serum and certain extracellular fluids in man. Am. J. Physiol., 153: 381, 1948.

5. Experimental myotonia and repetitive phenomena: The veratrinic effects of 2,4-dichlorphenoxyacetate (2,4-D) in the rat. Am. J. Physiol.. 155: 69, 1948.

6. Veratrinic effects of pentamethylenetetrazol (metrazol) and 2,2-bis (P-chlorophenyl) 1,1,1 trichloroethane (DDT) on mammalian neuromuscular function. Proc. Soc. Exp. Biol. Med., 70: 272, 1949.

7. A simple volumeter for measuring the oxygen consumption of small animals. Bull. Johns Hopkins Hosp., 84: 238, 1949.

8. On creatinuria in man. The roles of the renal tubule and of muscle mass. Bull. Johns Hopkins Hosp., 85: 370, 1949.

9. On certain effects of alpha-tocopheryl phosphate on oxidative mechanisms of striated muscle. Ann. New York Acad. Sci., 52: 180, 1949.

10. A reference base and system for analysis of muscle constituents. J. Biol. Chem., 182: 501, 1950.

11. Sex difference in the response of rats to sodium pentobarbital. Proc. Soc. Exp. Biol. Med., 74: 332, 1950.

12. Neuromuscular excitation: Responses of normal and denervated mammalian muscle to bis-trimethylammonium decane ($C_{10}$) and to d-tubocurarine. Am. J. Physiol., 162: 475, 1950.

13. A wide range mechano-electronic transducer for physiological applications. Rev. Sci. Instr., 22: 233, 1951.

14. Curarization of denervated muscle. Ann. New York Acad. Sci., 54: 337, 1951.

15. On certain aspects of the physiology of muscle _in_ The Musculo-skeletal System (Graduate Fortnight of the New York Academy of Medicine). Macmillan, New York, 1952, Chapter 3, 72-93.

16. Transfer rates across muscle membranes in man: Measure of blood flow and fluid compartments in skeletal muscle (abstr.). J. Clin. Invest., _30_: 684, 1951.

17. On muscular wasting of obscure origin and the thyroid gland. Bull. Johns Hopkins Hosp., _89_: 263, 1951.

18. Spread of excitation in skeletal muscle: Some factors contributing to the form of the electromyogram. Am. J. Physiol., _168_: 446, 1952.

19. Role of quaternary compounds in neural activity _in_ The Biology of Mental Health and Disease. Paul B. Hoeber, New York, 1952, Chapter 12, 162-177.

20. Measurement of limb blood flow in man by constant infusion of T-1824 (abstr.). Fed. Proc., _11_: 177, 1952.

21. Interrelations of magnesium with potassium, phosphorus and creatine in skeletal muscle of man. Trans. Assoc. Am. Phys., _65_: 223, 1952.

22. Interrelations of magnesium, potassium, phosphorus, and creatine in skeletal muscle of man. J. Clin. Invest., _31_: 850, 1952.

23. Alpha-tocopheryl phosphate and energy transfer in muscle. Proc. First and Second Medical Conferences of the Muscular Dystrophy Associations of America, Inc., p. 101.

24. Site of origin and velocity of propagation of fibrillary potentials of denervated muscle (abstr.). Fed. Proc., _12_: 235, 1953.

25. Dissimilation of glucose-1-phosphate and of fructose-1,6-phosphate by isolated rat diaphragm and by cell-free effluent from rat diaphragm. Bull. Johns Hopkins Hosp., _92_: 7, 1953.

26. On the mechanism of action of α-tocopheryl phosphate, with special reference to carbohydrate metabolism of striated muscle. I. Modification of epinephrine effect (hyperlactacidemia) by α-tocopheryl phosphate in the rat. Bull. Johns Hopkins Hosp., _92_: 26, 1953.

27. On the mechanism of action of α-tocopheryl phosphate, with special reference to carbohydrate metabolism of striated muscle. II. Effect on the capacity of rat diaphragm to dissimilate hexose phosphates. Bull. Johns Hopkins Hosp., 92: 32, 1953.

28. On the mechanism of action of α-tocopheryl phosphate, with special reference to carbohydrate metabolism of striated muscle. III. Inhibition of insulin-induced glycogenesis in isolated rat diaphragm. Bull. Johns Hopkins Hosp., 92: 41, 1953.

29. A metal-filled microelectrode. Science, 118: 22, 1953.

30. The myopathies: including their appearance in constitutional disease. Am. J. Med., 15: 829, 1953.

31. Measurement of blood flow and volume in the forearm of man; with notes on the theory of indicator-dilution and on production of turbulence, hemolysis, and vasodilatation by intra-vascular injection. J. Clin. Invest., 33: 482, 1954.

32. Origin and conduction of fibrillary potentials in denervated muscle. Abstr. XIX Intern. Physiol. Congr., Montreal, p. 493, 1953.

33. On the theory of the indicator-dilution method for measurement of blood flow and volume. J. Appl. Physiol., 6: 731, 1954.

34. Exchange of cations, respiratory gases and carbohydrate by intact human muscle (abstr.). J. Clin. Invest., 33: 915, 1954.

35. Site of origin and velocity of conduction of fibrillary potentials in denervated skeletal muscle. Am. J. Physiol., 178: 129, 1954.

36. A rapid spectrophotometric method for estimation of oxygen content of dog's blood. J. Appl. Physiol., 7: 577, 1955.

37. Metabolic exchange of human muscle in situ. Am. J. Physical Med., 34: 286, 1955 and Proc. 3rd Medical Conference of the Muscular Dystrophy Associations of America, New York, 1954, pp. 286-290.

38. Effect of stretch on metabolism of skeletal muscle (abstr.). Fed. Proc., 14: 93, 1955.

39. Skeletal muscle metabolism in man. Inadequacy of carbohydrate oxidation to account for resting oxygen consumption (abstr.). Fed. Proc., 14: 5, 1955.

40. Forearm metabolism in man. Inadequacy of carbohydrate oxidation to account for resting oxygen consumption (abstr.). J. Clin. Invest., 34: 920, 1955.

41. Loss of potassium from forearm of man under basal conditions (abstr.). Am. J. Physiol., 183: 593, 1955.

42. Factors which influence the movement of aldolase from excised rat diaphragm (abstr.). Am. J. Physiol., 183: 675, 1955.

43. Movement of aldolase from excised rat diaphragm. Am. J. Physiol., 185: 1, 1956.

44. Effect of potassium-rich medium, of glucose, and of transfer of tissue on oxygen consumption by rat diaphragm. Am. J. Physiol., 185: 12, 1956.

45. Carbohydrate metabolism of skeletal muscle in man during the night (abstr.). Fed. Proc., 15: 4, 1956.

46. Potassium effect of resting membrane potential of muscle in the intact rat (abstr.). Fed. Proc., 15: 88, 1956.

47. Movement of potassium into skeletal muscle during spontaneous attack in family periodic paralysis (abstr.). J. Clin. Invest., 35: 747, 1956.

48. The quantitatively minor role of carbohydrate in oxidative metabolism by skeletal muscle in intact man in the basal state. Measurements of oxygen and glucose uptake and carbon dioxide and lactate production in the forearm. J. Clin. Invest., 35: 671, 1956.

49. Carbohydrate metabolism in intact skeletal muscle in man during the night. J. Clin. Invest., 35: 991, 1956.

50. Effect of stretch on oxygen consumption of dog skeletal muscle in situ. Bull. Johns Hopkins Hosp., 99: 249, 1956.

51. Relationship between oxygen consumption and isotonic work in the dog (abstr.). Am. J. Physiol., 187: 597, 1956.

52. Effect of insulin on glucose uptake, lactate production and R.Q. in the forearm of man (abstr.). Am. J. Physiol., 187: 583, 1956.

53. Diseases of muscle in Biochemical Disorders in Human Disease, edited by R. H. S. Thompson and E. J. King. Academic Press, Inc., New York and J. and A. Churchill Ltd., London, 1957.

54. Effect of insulin on glucose uptake, lactate production and R.Q. in the forearm of man (abstr.). Clin. Res. Proc., 5: 14, 1957.

55. Effect of potassium on the resting membrane potential of skeletal muscle in the intact animal (abstr.). Clin. Res. Proc., 5: 18, 1957.

56. Muscle oxygen consumption and isotonic work in the dog (abstr.). Fed. Proc., 16: 35, 1957.

57. Net potassium movement between resting muscle and plasma in man in the basal state and during the night. J. Clin. Invest., 36: 723, 1957.

58. Movement of potassium into skeletal muscle during spontaneous attack in family periodic paralysis. J. Clin. Invest., 36: 730, 1957.

59. Increased permeability of muscle membranes produced by insulin (abstr.). J. Clin. Invest., 36: 938, 1957.

60. Diffusion of aldolase from rat skeletal muscle: An index of membrane permeability. Am. J. Physiol., 190: 201, 1957.

61. Increase in resting membrane potential of skeletal muscle produced by insulin. Science, 126: 1067, 1957.

62. Aldolase leak from muscle of mice with hereditary muscular dystrophy. Bull. Johns Hopkins Hosp., 102: 17, 1958.

63. Hyperosmolarity in adults: a critical review. J. Chronic Dis., 7: 1, 1958.

64. Increased muscle permeability to aldolase produced by insulin and by albumin. Am. J. Physiol., 192: 283, 1958.

65. Spontaneous and insulin-induced resistance of peripheral tissues to insulin in diabetes (abstr.). Clin. Res., 6: 250, 1958.

66. Changes in resting membrane potential of skeletal muscle in the intact rat produced by close arterial potassium infusion (abstr.). Clin. Res., 6: 305, 1958.

67. Stability of glucose uptake by human forearm despite increased arterial glucose concentration (abstr.). Fed. Proc., 17: 4, 1958.

68. Changes in muscle permeability to aldolase produced by altered metabolism and altered polarization (abstr.). Fed. Proc., 17: 174, 1958.

69. Increased muscle permeability to aldolase produced by depolarization and by metabolic inhibitors. Am. J. Physiol., 193: 534, 1958.

70. A pneumatic isotonic lever system for dog skeletal muscle. J. Appl. Physiol., 13: 307, 1958.

71. A simplified explanation of the theory of indicator-dilution for measurement of fluid flow and volume and other distributive phenomena. Bull. Johns Hopkins Hosp., 103: 199, 1958.

72. Production of very high extracellular potassium concentrations in the intact rat and its effect on muscle membrane potential (abstr.). The Physiologist, 1: 35, 1958.

73. Effect of blood flow on muscle oxygen consumption in the dog (abstr.). The Physiologist, 1: 36, 1958.

74. Muscle membrane as a dynamic structure and its permeability to aldolase. Ann. New York Acad. Sci., 75: 227, 1958.

75. Effect of insulin on resting potential and potassium content of rat muscle (abstr.). Fed. Proc., 18: 175, 1959.

76. Hyperpolarization of muscle induced by insulin in the absence of glucose (abstr.). J. Clin. Invest., 38: 1057, 1959.

77. The significance of the action of insulin upon muscle membrane potential. Diabetes, 8: 318, 1959.

78. Effect of insulin on membrane potential and potassium content of rat muscle. Am. J. Physiol., 197: 515, 1959.

79. Hyperpolarization of muscle by insulin in a glucose-free environment. Am. J. Physiol., 197: 524, 1959.

80. Effect of partial venous occlusion and release on muscle oxygen uptake and blood flow (abstr.). Fed. Proc., 19: 94, 1960.

81. Insulin effect on muscle potassium flux (abstr.). Fed. Proc., 19: 163, 1960.

82. Effect of insulin on potassium efflux from rat muscle in the presence and absence of glucose. Am. J. Physiol., 198: 1066, 1960.

83. Dependency of oxygen consumption of skeletal muscle upon the number of stimuli during work in the dog. Am. J. Physiol., 198: 1333, 1960.

84. The poorly-permeable membrane as an alternative to the carrier hypothesis of facilitated diffusion (abstr.). J. Clin. Invest., 39: 1042, 1960.

85. Metabolism of free fatty acids (FFA) by forearm tissues in man (abstr.). The Physiologist, 3: 9, 1960.

86. Mechanism of muscle contraction and its energetics in Bard's Medical Physiology. The C. V. Mosby Co., St. Louis, 1961.

87. Potassium flux and further observations on aldolase flux in dystrophic mouse muscle. Bull. Johns Hopkins Hosp., 108: 208, 1961.

88. Metabolic and circulatory effects of epinephrine in the forearm of man (abstr.). J. Clin. Invest., 40: 1022, 1961.

89. Forearm metabolism in obesity and its response to insulin (abstr.). The Physiologist, 4: 89, 1961.

90. A model of a poorly-permeable membrane as an alternative to the carrier hypothesis of cell membrane penetration. Bull. Johns Hopkins Hosp., 109: 35, 1961.

91. Theory of the use of arteriovenous concentration differences for measuring metabolism in steady and non-steady states. J. Clin. Invest., 40: 2111, 1961.

92. Forearm metabolism in obesity and its response to intra-arterial insulin. Evidence for adaptive hyperinsulinism. The Lancet, II: 690, 1961.

93. Effect of insulin on carbohydrate metabolism and on potassium in the forearm of man. J. Clin. Invest., 41: 108, 1962.

94. Heterogeneity of forearm metabolism with special reference to free fatty acids. J. Clin. Invest., 41: 116, 1962.

95. Circulation times and the theory of indicator-dilution methods for determining blood flow and volume in Handbook of Physiology Section 2. Circulation. Vol. 1, Chapter 18. Published by the American Physiological Society, 1962.

96. Theoretical basis of indicator-dilution methods for measuring flow and volume. Circ. Res., 10: 393, 1962.

97. Effect of insulin on free fatty acid metabolism in the human forearm (abstr.). Fed. Proc., 21: 200, 1962.

98. Dissociation of insulin action in the forearm of man (abstr.). J. Clin. Invest., 41: 1393, 1962.

99. Forearm metabolism in acromegaly (abstr.). Forty-fourth meeting, The Endocrine Society, Abstract 63, p. 31, June, 1962.

100. Diseases of muscle in Biochemical Disorders in Human Disease, edited by R. H. S. Thompson and E. J. King. Academic Press, Inc., New York and J. and A. Churchill Ltd., London, 1963.

101. Blood flow through and oxygen consumption by dog skeletal muscle during and following partial venous occlusion. Am. J. Physiol., 203: 470, 1962.

102. Preservation of insulin effect on FFA movement in hypophyseal-adrenocortical-dependent insulin resistance (abstr.). The Physiologist, 3: 197, 1962.

103. Forearm metabolism in obesity and its response to intra-arterial insulin. Characterization of insulin resistance and evidence for adaptive hyperinsulinism. J. Clin. Invest., 41: 2173, 1962.

104. Role of free fatty acids in forearm metabolism in man, quantitated by use of insulin. J. Clin. Invest., 41: 2191, 1962.

105. Effect of circulatory beds on tracer experiments, or non-compartmental analysis. Ann. New York Acad. Sci., in press.